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| 09/909,460 | 07/18/2001 | Lynn B. Lunsford | 08191-014002 | 1198 |

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| EXAMINER | |
|---|---|
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| ART UNIT | PAPER NUMBER |
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DATE MAILED: 01/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/909,460 | Applicant(s) Lunsford |
|---|---|---|
| | Examiner Dave Nguyen | Art Unit 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *Nov 8, 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above, claim(s) *17, 22, 24, 25, 27-32, and 37-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 18-21, 23, 26, 33-36, and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *Oct 18, 2001* is/are a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some* c)☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3 and 1(*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election without traverse the claimed invention of Group I, the species B/: a DNA encoding a peptide which binds to an MHC class I molecule, the species anionic lipid, and the species sequence which trafficks to endoplasmic reticulum in the response filed October 17, 2000 is acknowledged.

Applicant's election with traverse the claimed invention of claim 51 in the response filed November 8, 2002 is also acknowledged. The traversal is found persuasive, and thus, the claimed invention of claim 51 belongs to Group I claims and will be examined together with claimed invention of Group I.

Claims readable on non-elected invention, claims 37-50, and claims directed to non-elected species, *e.g.,* claims 17, 22, 24, 25, 27-32 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Elected claims 1-16, 18-21, 23, 26, 33-36, 51 are pending for examination.

Claims 8, 23, encompassing an amino acid sequence that differs by no more than 25% from the sequence of a naturally occurring peptide recognized by a T cell and is recognized by the T cell, claims 34-36 encompassing a method of generating a mucosal immunity in a mucosal tissue of any animal intended for a real-world therapeutic DNA treatment, and claims 34 and 51 encompassing a gene therapy method of administering any DNA for the purpose of generating a therapeutically relevant effect in any animal, *e.g.,* reptiles, birds, mammals, amphibians, wherein any administration route including oral administration, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

1/ The microparticle of claim 8, wherein the expression product is selected from the group consisting of:

a/ a polypeptide with at least 7 amino acid in length, having a sequence identical to the sequence as cited in any of (i) – (iv) of claim 8;

b/ a peptide as cited in (b) of claim 8;

c/ a polypeptide as cited in (c) of claim 8;

d/ any of a/, b/, or c/ linked to a trafficking sequence.

2/ A method for generating an immune response against an antigen in a mammal, the method comprising:

- Delivering an effective amount of microparticles less than about 20 microns comprising a polymeric matrix, a lipid; and a nucleic acid encoding an antigen into a mammal, thereby generating an immune response against said antigen;

3/ A method of introducing a DNA directly to a target site of a mammal, the method comprising: introducing directly an effective amount of microparticles less than about 20 microns comprising a polymeric matrix, a lipid; and a nucleic acid into the target site of a mammal.

The specification does not reasonably provide an enablement for claims directed to the subject matter being sought in claim 23, and any DNA delivery method which encompasses the use of any therapeutic DNA in any animal.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not reasonably provide enablement for any other *in vivo* DNA delivery method within the context of therapeutic applications, wherein any administration route is employed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification provides factual evidence demonstrating intraperitoneal, intramuscular, or subscutaneous injection of microparticles comprising a polymeric matrix and a nucleic acid encoding a VSV-N peptide (VSV-Npep) generates an enhanced CTL response in mice relative to controls, *e.g.*, recombinant VSV-N, microparticles/DNA that does not encoded the VSV-Npep. However, the specification fails to provide factual evidence demonstrating how one skilled in the art reasonably extrapolates from the

data obtained from the working examples to any or all gene therapy methods using a non-immunogenic product which is encoded by a DNA employed in the gene therapy method as claimed, particularly since the application does not provide a sufficient guidance as to what are exactly the "non-immunogenic product" that would generate a "useful" effect from the gene therapy methods as claimed. Given that gene therapy remains unpredictable at the time the invention was made (Anderson, 1998, Verma, 1997), it is not apparent how one skilled in the art determines, without undue experimentation, as to which of the "non-immunogenic" encoded DNA are "useful" in the gene therapy method as claimed, particularly on the basis of applicant's disclosure.

Major considerations for any gene transfer or nucleic acid therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the treatment in a treated subject (Anderson (Nature, Vol. 392, 25-30, April 1998). More specifically, Anderson teaches that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph), that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types. Verma *et al.* (Nature, Vol. 389, 18, pp. 239-242, September 1997) also states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph).

Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Even in 2000, Li, Gene Therapy, 7, 31-34, 2000, states:

> The science of nonviral gene delivery is still in its infancy. Further improvement of the delivery system will continuously rely on a better understanding of the cellular and *in vivo* barriers in gene transfer (page 34).

On the basis of transient gene expression and the doubts expressed by the art of record, the specification does not provide sufficient guidance and/or factual evidence demonstrating a reasonable correlation between the disclosure including its exemplified examples and the subject matter being sought in the claims. Thus, it is not apparent how one skilled in the art determines, without undue experimentation, which of the disclosed DNA pharmaceutical kits generate a therapeutic effect in any and/or all gene therapy methods, nor is it apparent as to how one skilled in the art reasonably extrapolates from the *in vitro* delivery of a probe as exemplified by the specification to any and/or all pharmaceutical products as recited in the presently pending claims, particularly given the unpredictability of gene therapy and/or the doubts expressed in the art of record. Furthermore, the specification contemplates that any synthetic antigen encoded by a DNA entrapped within a polymeric matrix, wherein the antigen only is required to exhibit an "essential", 25% or 50% identity to a naturally occurring peptide or protein fragment, when used in any *in vivo* delivery method in any animal, would provide a desired therapeutically relevant effect. However, it is not apparent as to how one skilled in the art identifies and/or determines, without any undue experimentation, as to which DNA coding for "essentially identical amino acid sequence" is effective for use in an *in vivo* nucleic acid therapy method as claimed. The problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules.

Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable (see Ngo *et al.,* in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.,* (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). In addition of the lack of reasonable correlation between a therapeutically relevant effect of a naturally occurring peptide or protein known in the prior art and that of a synthetic peptide as contemplated by the claimed invention, one skilled in the art must also has to overcome the unpredictability of *in vivo* nucleic acid delivery methods within the context of therapeutic applications, as expressed by the art of record. Furthermore and even with DNA immunization methods, the state of the art exemplified in McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

In addition, Brayden *et al.* (Microbes and Infection, Vol. 3, 867-876, 2001 states:

Programmed oral immunization using particulate systems still remains as elusive as it did in the mid-late 1980s. Nature has provided many examples of proof of principle of the ability of particles to be absorbed. However, there is still very little known about how human M Cells function towards synthetic

formulations in respect to particle uptake and subsequent immunity. Predictions on particle uptake and immune outcome for human oral studies cannot be made with any confidence using dat from other species. It is also apparent that M-cell –targeting agents possibly in combination with adjuvants will probably be required to increase antigen-loaded particle uptake and to induce the immunological mucosal and systemic response to adequate levels.....Finally, while nasal immunization with antigens entrapped in particles has yielded more encouraging data than oral immunization thus far in both animal and human studies, this data should be interpreted with caution due to an inherent bias in mice arising from favourable physiological features (page 873, column 2).

As such, it is not apparent how a skilled artisan would reasonably extrapolate from applicant's specification and its guidance to a method of employing any DNA/lipid complex contained in a microparticle to generate a therapeutically relevant mucosal immunity in any animal intended for a real-world treatment. At best, the specification coupled with the state of the prior art of record only provides reasonable enablement for the claimed embodiments as indicated at page 2 of the this Office action.

Thus, the specification is not enabling under 35 U.S.C. 112, first paragraph, for any and/or therapeutic nucleic acid constructs within the context of treatment and/or prevention of any disease in any subject, and for the claimed subject matter being sought for the "essential identity" and for claim 23, particularly on the basis of applicant's disclosure and the reasons stated in the art of record.

***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-7, 34, 51 are rejected under 35 U.S.C. 102(e) as being anticipated by Roth *et al.* (US Pat No. 5,879,713).

Roth *et al.* teach a direct transfection method of employing a plurality of microparticles comprising a polymeric matrix, a lipid, a plasmid DNA coding for a protein of interest and a stabilizer compound, wherein the liposome complexed with the DNA is encapsulated within the microparticles, *e.g.,* column 3, lines 5-14, 40-61; entire column 6; column 7, lines 31-67; column 9, lines 1-9; column 9 bridging column 10; and columns 15 to 16.

Absent evidence to the contrary, the plasmid DNA and the microparticles of Roth *et al.* have all of the properties cited in the claims.

Claims 1, 5, 6, 8-16, 18-21, 23, 26, 33-36, 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roth *et al.* taken with Jones *et al.* (Int'l Meeting on Nucleic Acid Vaccines, 1996), and further in view of any of Hedley *et al.* (US Pat No. 5,783,567) and Hedley II (WO 98 31398) wherein Curley and Langer constitute as "another" in both Hedley references.

Roth *et al.* is applied here as indicated above. Roth *et al.* does not teach specific limitations including the use of a targeting molecule linked to the nucleic acid, stabilizers compounds including carbohydrates, specific lipid compounds including CTAB, phospholipid and phosphatidylcholine, the ratio of latic acid to glycolic acid in the copolymer and the use of a proteinaceous antigenic determinant in preparation of microparticles/lipid/DNA complexes.

However, at the time the invention was made, Jones teaches a method of employing microparticles having a diameter of no more than 10 ug composed o PLGA for delivering supercoiled plasmid DNA coding for any immunogenic protein known in the prior art (entire document). Route of administration including delivery into a mucosal tissue is also taught in Jones. Jones also teaches ratio by weight that encompasses the ratios employed in the as-filed specification.

In addition, Hedley and Hedley II are cited to indicate that preparations of supercoiled plasmid DNA entrapped within a polymeric matrix wherein the use of a targeting molecule linked to a nucleic acid coding for a MHC-I binding antigenic peptide, stabilizers compounds including carbohydrates, specific lipid compounds including CTAB, phospholipid and phosphatidylcholine, the ratio of latic acid to glycolic acid in the copolymer, the use of an endoplasmic reticulum (ER) directed peptide and the use of a proteinaceous antigenic determinant are incorporated in the preparations are known in the prior art at the time the invention was made, *e.g.,* (Hedley, entire front page of the patent which cites prior art that teach DNA immunization methods and MHC-I binding peptides), columns 5-8, 10, 11 and columns 61-64; Hedley II, entire document, especially pages 12, 17, 21, 39, 52 and 81-90.

It would have been obvious for one of ordinary skill in the art to have employed any known DNA coding for MHC-I binding antigenic peptide in the preparations of microparticles described in Roth for use in a DNA immunization method at any desired tissue so as to elicit an immune response in a mammal. One of ordinary skill in the art would have been motivated to have employed any MHC-I binding peptide encoded DNA known in the prior art and any known polymeric microparticle with size of no more than 10 um in the DNA/microparticles preparation of Roth because Jones teaches that polymeric microparticles with size of no more than 10 um are effective for *in vivo* DNA delivery methods at any desired tissue wherein a DNA coding for any immunogen is employed so as to elicit an immune response including mucosal immunity in a mammal.

It would also have been obvious for one of ordinary skill in the art to have employed or incorporated stabilizer compounds, two or more expression cassettes encoding two distinct and/or overlapped MHC-I binding peptides, antigenic protein sequences and/or immune response regulators, specific lipid

compounds including CTAB, phospholipid and phosphatidylcholine, the ratio of latic acid to glycolic acid in the copolymer or an endoplasmic reticulum (ER) directed peptide in the preparations of microparticles described in Roth for use in a DNA transfection method. One of ordinary skill in the art would have been motivated to have employed known enhancers and/or stabilize compounds and/or targeting peptide sequences and/or two or more expression cassettes in the preparations of Roth because such modifications are routinely employed in the art of making lipids and/or polymers for use as a carrier for enhancing the delivery of a DNA into the cytosol of a target cell, as evidenced by the disclosures and references cited in both Hedley and Hedley II.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-16, 18-21, 23, 26, 33-36, 51-53 and 55-73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 of US patent No. 5,783,567 taken with Roth, Jones (cited above), and application's admission over the prior art on page 40 of the as-filed specification.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are readable on a polymeric composition comprising a polymer microparticle, and DNA, wherein the polymeric microparticle is less than about 20 microns, and method of using the polymeric composition to deliver an encoded DNA molecule to a subject.

To the extent that the claims of the Patent does not claim the use of a lipid compound including anionic lipid compound in the microparticle preparation, it would have been obvious to one of ordinary skill in the art that claims readable on lipid contained microparticles are obvious variants of the claims cited in the Patent because Roth *et al.* teach a direct transfection method of employing a plurality of microparticles comprising a polymeric matrix, a lipid, a plasmid DNA coding for a protein of interest and a stabilizer compound (buffer containing stabilizer compounds), wherein the liposome complexed with the DNA is encapsulated within the microparticles, because Jones teaches that polymeric microparticles with size of no more than 10 um are effective for *in vivo* DNA delivery methods at any desired tissue wherein a DNA

coding for any immunogen is employed so as to elicit an immune response including mucosal immunity in a mammal, and because negative charged lipids are routinely employed in the prior art as carrier for biologically active molecules.

Wheeler (Gene Therapy, 6, 721-281, 2/1999) and Wheeler *et al.* (US 2002/0192651) are prior art which also teach that a stabilized plasmid lipid particle coated by a hydrophilic polymer, *e.g.,* PEG, are effective carriers of nucleic acids for non-viral nuclei acid delivery.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Kimberly Davis, whose telephone number is **(703) 305-3015**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

DAVE T. NGUYEN
PRIMARY EXAMINER

Dave Nguyen

Patent Examiner

Art Unit: 1632